REMARKS

Claims 1, 3-17, 19-68, and 70 are currently pending in the application. Claim 7 is amended. No new matter is added.

Formal Matters

Applicant wishes to thank Examiner Gambel for the telephone interview of March 30, 2005 with Applicant's representatives. Applicant submits that the subject matter of the interview is incorporated into the following response.

Additionally, Applicant acknowledges the withdrawal of the prior rejections under 35 U.S.C. §102(e) and §103(a), and thank the Examiner for his close attention to the patentability of the instant claims.

Rejection of Claim 7 Under 35 U.S.C. §112, Second Paragraph

The Examiner has rejected claim 7 for lack of proper antecedent basis. Applicant has amended claim 7 to properly recite dependence from claim 5, and submits that the rejection is now moot. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1, 3-14, 17, 21-26, 28, 29, and 70 Under 35 U.S.C. §103(a)

The Examiner has rejected claims 1, 3-14, 17, 21-26, 28, 29, and 70 under §103(a) as being obvious over the combination of Grossmann et al. and Kato et al., in view of Maraskovsky et al., Dullforce et al., Heath et al., McHugh et al., Jacquier-Sarlin et al., and in further view of the teaching in the specification regarding engineering attachment of a lipid to a molecule to permit stable association in the cell plasma membrane.

The Examiner asserts that Grossmann et al. teach transgenic expression of CD40L in neuro-2a tumor cells, wherein the CD40L acts as a costimulator. The Examiner asserts that Kato et al. teach that CD40-CD40L interaction plays a critical role in immune activation. The Examiner admits, however, that the teachings of Grossman et al. and Kato et al. differ from the

claimed invention in that **neither reference teaches admixing a ligand for CD40 which comprises a heterologous cell membrane binding moiety**.

The Examiner asserts that Maraskovsky et al. teach a method of vaccination with antigen-expressing activated dendritic cells, including stimulating immune responses with the administration of other cytokines such as the CD40 ligand. The Examiner notes that Maraskovsky et al. do not teach the administration of agonistic CD40-specific antibodies. The Examiner asserts that each of Dullforce, Heath, and Caux teach anti CD40 antibodies which are capable of stimulating immune responses. The Examiner implies that it would have been obvious to one of skill in the art to combine the teachings of anti-CD40 antibodies as taught by Dullforce, Heath, and/or Caux with the "antigen" expressing activated dendritic cells as taught by Maraskovsky to arrive at the present invention. The Examiner also cites McHugh et al as teaching methods of introducing the T-cell co-stimulatory molecule B7 into a tumor cell membrane via glycosyl-phosphatidylinositol (GPI). The Examiner asserts that even though McHugh et al focus on tumor immunity, one of skill in the art would have been motivated to employ GPI-anchored co-stimulatory molecules with immunogenic cells to stimulate immune responses of interest. Applicants respectfully disagree.

For the reasons described below, the Examiner has failed to establish a *prima facie* case of obviousness under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. *Id.* The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. *Id.* Finally, the prior art reference (or references when combined) must teach or suggest *all the claim limitations*. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

The CD40 ligand-specific references do not teach each element of the claimed invention

Regardless of how combined, the teachings of Grossmann et al. and Kato et al., in view of Maraskovsky et al., Dullforce et al., Heath et al. do not teach a method of vaccinating a mammal to an antigen by administering a cell (comprising the antigen) in admixture with a ligand for CD40 which includes a heterologous cell membrane binding moiety. None of Grossmann et al. and Kato et al., Maraskovsky et al., Dullforce et al., or Heath et al., regardless of how combined, teach a membrane associated ligand for CD40. Moreover, Maraskovsky et al. teaches only soluble immunostimulatory molecules and does not teach or even suggest membrane bound immunostimulatory molecules, or that membrane attachment should or could be attempted.

There is no motivation to combine the CD40 ligand references with the teachings of McHugh et al.

The teachings of McHugh et al. focus on elucidating the second signal required of T-cells for cell-mediated immunity (the first signal being engagement of the T-cell receptor with peptide-bearing MHC molecules). Applicant submits that McHugh teaches a construct comprising a GPI moiety fused to B7 molecules (also referred to as CD80), and the use of the fusion protein, incorporated into the membrane of tumor cells, to provide a costimulatory signal needed to stimulate T cells. Applicants submit that not only does McHugh not teach or even suggest the use of a GPI moiety linked to CD40 ligand (i.e., an engineered CD40 ligand), or the use of such an engineered CD40 ligand in a mixture with an antigen bearing cell for the purpose of vaccinating a mammal, but McHugh also acknowledges that the specific teachings relating to GPI-B7 are unpredictable. The Examiner asserts that one of skill in the art would have been motivated to create membrane linked anti-CD40 antibodies to mix with the activated dendritic cells of Maraskovsky, despite Maraskovsky's teaching that the cytokine should be **soluble**, and in view of the acknowledgment in McHugh that the GPI linked system **may differ from system to system**. In addition, McHugh et al. teach that B7 may by the "crucial second signal *in vivo*" for T-cell mediated immune responses; that is, McHugh et al. teaches that the immunostimulatory effect observed in the experiments taught therein may be specific for B7. When viewed together, the combined teachings of Grossmann et al. and Kato et al., Maraskovsky et al., Dullforce et al., or Heath et al., regardless of how combined, provide no

motivation to seek out a method for membrane attachment of an anti-CD40 antibody (or CD40 ligand). Likewise, the teachings of McHugh et al. provide no motivation to stray away from the "crucial second signal" provided by B7 by substituting B7 with CD40 ligand or an anti-CD40 antibody, particularly since neither of these ligands for CD40 are even mentioned in McHugh et al.

Although the instant claims are under examination for the elected species of an anti-CD40 antibody, applicants submit that even when given their full claim scope (i.e., including CD40 ligand) the references cited by the Examiner do not render the invention obvious. As noted above, none of the references drawn to ligands for CD40 teach a ligand having a heterologous cell membrane binding moiety. In addition, McHugh teaches that the GPI moiety is to be coupled to the C-terminal end of a desired protein for incorporation into the cell membrane. Applicants submit, however that, as shown in Exhibit A (GenBank Accession No P29965; filed with Applicant's response of April 7, 2003), the C-terminus of the CD40 ligand is extracellular. That is, it is the C-terminus of the CD40 ligand which is likely to bind to CD40. Since, as taught by McHugh, GPI moieties link to the carboxy-terminus of proteins, one of skill in the art would expect that the attachment of a GPI moiety to the C-terminus of CD40 ligand would interfere with the binding of CD40 ligand to its receptor. Thus, one of skill in the art would not have been motivated, absent the teachings of the present invention, to modify a CD40 ligand by attaching a carboxy-terminal GPI moiety.

With respect to the Examiner's assertion that the required motivation to combine the teachings of the cited references is provided by the specification's disclosure that it was well known to engineer the attachment of a lipid to a molecule such as a peptide to permit the complex to be stably associated with a cell membrane, Applicant respectfully submits that the Examiner is in error. Applicant submits that it is well established law that the level of skill in the art (e.g., the technique for modifying a CD40 ligand to include a cell membrane binding moiety) cannot be relied upon to provide the suggestion to combine references (*Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999)). Thus, the mere fact that the technology existed to modify a protein to be incorporated into a cell membrane does not provide the level of motivation necessary to make the combination suggested by the Examiner.

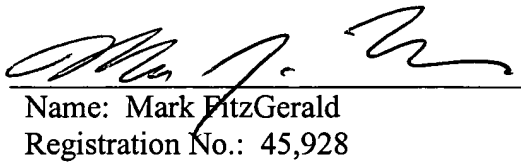
The Examiner has also cited Jacquier-Sarlin et al., which teaches the use of complement fragments including C3b to enhance immune responses to antigens of interest, as rendering claims 3 and 4, drawn to including with the CD40 ligand-enhanced cell of claim 1, an opsonin-enhanced cell. Applicant respectfully disagrees with the Examiner. Jacquier-Sarlin merely teaches the ability of the complement fragment C3b to modulate antigen processing, and then **only when fused to the antigen**. There is no requirement in the instant claims for fusion of an opsonin to an antigen of interest, only that the vaccine composition include an opsonin-enhanced cell (defined at page 3 of the specification as "cells which have been 1) modified so as to express an opsonin from a recombinant nucleic acid, 2) modified so as to express higher levels of an endogenous opsonin, or 3) mixed with an exogenous opsonin"). Jacquier-Sarlin et al. do not teach an opsonin-enhanced cell, and moreover does not teach or even suggest a CD40 ligand-enhanced cell of the present invention. Likewise, because none of the other references cited by the Examiner, regardless of how combined, teach or suggest a CD40 ligand-enhanced cell as claimed, even if combined with the teachings of Jacquier-Sarlin et al., the combined teachings still do not provide a CD40 ligand-enhanced cell as claimed and, further, do not teach, vaccine composition comprising an opsonin-enhanced cell in addition to a CD40-ligand enhanced cell.

Accordingly, Applicant submits that the invention is not obvious over the teachings of Maraskovsky et al., Dullforce et al., Heath et al., Caux et al., Jacquier-Sarlin et al., and/or McHugh et al. because there are no teachings in these references, alone or taken together, to motivate one of skill in the art to make the claimed invention. Applicant therefore requests that the rejection be reconsidered and withdrawn.

Applicant submits that all claims are allowable as written and respectfully request early favorable action by the Examiner. If the Examiner believes that a telephone conversation with Applicant's attorney/agent would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned attorney/agent of record.

Respectfully submitted,

Date: April 4, 2005



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